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SYSTEMATIC REVIEWS AND META-ANALYSES

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Ursodeoxycholic Acid and Diets Higher in Fat Prevent Gallbladder Stones During Weight Loss: A Meta-analysis of Randomized Controlled Trials

Caroline S. Stokes,[*] Lise Lotte Gluud,[‡] Markus Casper,[*] and Frank Lammert[*]

[*]Department of Medicine II, Saarland University Medical Center, Homburg, Germany; and [‡]Diabetes Research Division, Department of Medicine, Gentofte Hospital, University of Copenhagen, Hellerup, Denmark

This article has an accompanying continuing medical education activity on page e61. Learning Objectives—At the end of this activity, the successful learner will be able to recognize the role of ursodeoxycholic acid in preventing primary gallbladder stones from forming during weight loss.

BACKGROUND & AIMS: **The prevalence of gallstones is increasing in association with the obesity epidemic, but rapid weight loss also increases the risk of stone formation. We conducted a systematic review of the efficacy of strategies to prevent gallbladder stones in adults as they lose weight.**

METHODS: **Randomized controlled trials of nonsurgical strategies to prevent gallstones were identified by electronic and manual searches. Our final analysis included 13 trials, comprising 1836 participants undergoing weight loss through dieting (8 trials) or bariatric surgery (5 trials). The trials compared ursodeoxycholic acid (UDCA) or high-fat weight loss diets with control interventions. We performed random-effects meta-analyses and evaluated heterogeneity and bias with subgroup, sensitivity, regression, and sequential analysis.**

RESULTS: **UDCA reduced the risk of ultrasound-verified gallstones compared with control interventions (risk ratio, 0.33; 95% confidence interval [CI], 0.18–0.60; number needed to treat, 9). This effect was significantly larger in trials of diets alone (risk ratio, 0.17; 95% CI, 0.11–0.25) than in trials of patients who underwent bariatric surgery (risk ratio, 0.42; 95% CI, 0.21–0.83) (test for subgroup differences, $P = .03$). UDCA reduced the risk of cholecystectomy for symptomatic stones (risk ratio, 0.20; 95% CI, 0.07–0.53). Diets high in fat content also reduced gallstones, compared with those with low fat content (risk ratio, 0.09; 95% CI, 0.01–0.61). The meta-analyses were confirmed in trials with a low risk of bias but not in sequential analysis. No additional beneficial or harmful outcomes were identified.**

CONCLUSIONS: **On the basis of a meta-analysis of randomized controlled trials, during weight loss, UDCA and/or higher dietary fat content appear to prevent formation of gallstones.**

Keywords: Bariatric Surgery; Cholelithiasis; Cholesterol; Obesity.

The prevalence of gallstones is currently between 10% and 20% in Western adults, with a projected rise because of the obesity epidemic and increase in metabolic syndrome and aging population.[1–3] An estimated 25% of gallstone carriers develop symptoms and complications such as cholecystitis, cholangitis, and pancreatitis.[4] Patients with symptomatic gallstones frequently require hospital admission and laparoscopic cholecystectomy. Annually more than 700,000 cholecystectomies are performed in the United States, which are not only associated with specific complications such as bile duct injury but also fatty liver disease[5] and represent a major economic burden on healthcare resources.[6]

Gallbladder stones comprise the common cholesterol stones and black pigment stones.[7] Currently more than 30% of Americans are obese,[8] and in particular, abdominal obesity is an established risk factor for cholesterol stones, because it promotes insulin resistance and biliary cholesterol hypersecretion.[9,10] A study in more than 90,000 women reported a 7-fold risk of gallstones in morbidly obese compared with normal weight populations.[11] However, cholesterol stones also frequently

Abbreviations used in this paper: **BMI, body mass index; CI, confidence interval; CSI, cholesterol saturation index; LCD, low calorie diet; NNT, number needed to treat; RCT, randomized controlled trial; RR, risk ratio; UDCA, ursodeoxycholic acid; VLCD, very low calorie diet; WMD, weighed mean difference.**

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occur after rapid weight loss as a result of gallbladder hypomotility, and cholesterol supersaturation of bile as a result of reduced biliary bile salt secretion and enhanced mobilization of cholesterol.[12–15] During weight-reduction dieting, gallstones may develop after just 4 weeks.[15] Currently, no consensus exists with regard to gallstone prevention in obese patients undergoing weight reduction by bariatric surgery. Prophylactic cholecystectomy is often proposed for these individuals,[16] although the risk of developing symptomatic gallstones might be moderate.[17] However, obese patients undergoing gastric bypass surgery with concomitant cholecystectomy not only have a risk of postoperative complications but often require longer hospital stays.[18,19]

Lifestyle interventions such as physical activity or dietary fat manipulation during dieting have been investigated for gallstone prevention because of their capacity to promote gallbladder motility.[20] Clinical studies with bile acids, in particular ursodeoxycholic acid (UDCA), have demonstrated a decrease of bile lithogenicity through reducing the intestinal absorption and biliary secretion of cholesterol as well as shifting the phase separation of bile toward solubilization in micelles and vesicles.[21,22] A seminal randomized controlled trial[23] (RCT) in only 68 obese patients reported a reduced risk of gallstone formation with UDCA administration during weight loss on a very low calorie diet (VLCD). This finding was corroborated in further RCTs,[24,25] although others found no effect of UDCA on gallstone prevention during weight loss.[26,27] A meta-analysis of 5 RCTs after bariatric surgery reported a protective effect of UDCA against gallstones during weight loss[28] but did not evaluate trials using diet alone, and it did not assess for differences in weight loss after dieting only compared with surgery.

Nonsurgical preventions for primary gallstones need greater consideration, particularly because the American Medical Association recently declared that obesity should be categorized as a disease, requiring medical prevention and treatment.[29] Therefore, an increase in individuals at risk for gallbladder stones is to be expected. Because most RCTs with nonsurgical interventions include few patients and their combined effect is unclear, we conducted a systematic review and meta-analysis of RCTs to investigate the efficacy of nonsurgical preventive options for gallbladder stones in adults during weight loss after bariatric surgery or with diet alone.

Methods

The systematic review and meta-analyses were performed according to a published protocol[30] and followed the instructions in the *Cochrane Handbook for Systematic Reviews of Interventions*.[31,32] The main objective was to evaluate the nonsurgical primary prevention of gallbladder stones, focusing on trials in patients undergoing intended weight loss. Our primary outcome measures were formation of ultrasonically verified gallstones, mortality, and adverse events. Secondary outcome measures included quality of life, cholecystectomy, bile lithogenicity (defined as changes in physiological parameters of bile composition indicative of an increased risk of gallstones, eg, cholesterol saturation index [CSI],[33] nucleation time for cholesterol crystal formation,[34] or presence of cholesterol crystals) and weight loss (reduction in body weight assessed in kilograms or by using the body mass index [BMI]). Interventions were included irrespective of the dose or class of drug. The control groups included placebo, no intervention, or pharmacologic and non-pharmacologic interventions. The threshold for duration of therapy was set to a minimum of 4 weeks.[15,35] Quasi-randomized trials and observational studies were only eligible for inclusion in the analyses of adverse events.

Search Strategy for Identification of Trials

We identified eligible RCTs through electronic and manual searches. Male and female adults (older than 18 years of age) were included irrespective of ethnicity. Participants were eligible for inclusion if they did not have gallbladder stones at baseline verified by ultrasonography. We searched the Cochrane Hepato-Biliary Group Controlled Trials Register,[32] the Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library*, MEDLINE, EMBASE, and Science Citation Index Expanded. The search was performed in each database from time of inception until July 2013 (Supplementary Table 1).

Trial registries were scanned in 2 search portals, the U.S. National Institutes of Health (www.clinicaltrials.gov) and the World Health Organization International Clinical Trial Registry Platform (www.who.int/ictrp/search/en/). We originally planned to include unpublished trials, but no such trial was identified. The manual search comprised scanning reference lists of relevant articles.

All references identified in the searches were reviewed, and potentially eligible trials were listed and compared against the inclusion criteria. Excluded trials were listed with the reason for exclusion. All authors agreed on the final inclusion of trials. Three authors extracted data independently by using standardized forms (M.C., L.G., and C.S.) and resolved disagreements through discussion. Authors of individual trials were contacted for any unclear or missing information. Two trials were translated into English before the data extraction.

Assessment of Bias

Trials were assessed by using the Cochrane Collaboration risk of bias tool.[31] Information was extracted for each trial by at least 2 authors, and risk of bias was rated as low or high (unlikely or likely to significantly influence the results) or unclear with regard to the following

domains: selection bias (including allocation sequence generation and allocation concealment), detection and performance bias, attrition bias, reporting bias, and other biases such as premature termination of trials for which predefined criteria were not specified.[31]

Statistical Analysis

The data were analyzed by using the Cochrane Review software, Review Manager 5, STATA 12 (Stata Corp, College Station, TX) and Trial Sequential Analysis (Copenhagen Trial Unit, Copenhagen, Denmark). The primary meta-analyses were performed by using random-effects models because of expected clinical heterogeneity. Different interventions were analyzed separately. Fixed-effect models were used to evaluate the robustness of the results but were only reported if they differed from that of the random-effects models. The measures of treatment effect were expressed as risk ratios (RRs) for dichotomous data and weighted mean differences (WMDs) for continuous outcomes, both with 95% confidence intervals (CIs) and with I^2 as markers of heterogeneity. The number needed to treat (NNT) was computed for dichotomous data when the CI did not cross one. When trials included more than 2 intervention groups, multiple groups were combined to create a single pair-wise comparison.[31] Data on all participants randomized (irrespective of compliance or follow-up) were sought to allow intention-to-treat analyses.

The risk of small study effects was analyzed through regression analyses (Egger test). We performed the following subgroup analyses to evaluate the influence of participant type (type of weight loss method), treatment dose (medium-to-high or low-dose UDCA, ie, 1000–1200 or 500–750 mg, respectively), initiation of UDCA in the bariatric surgery trials, and risk of bias (low versus high or unclear risk). Sensitivity analyses evaluated the importance of losses to follow-up (poor outcome analyses assuming that losses to follow-up were treatment failures and good outcome analyses assuming they were treatment successes). We also repeated the analyses with the 0.5 continuity correction to provide imputed data for analysis in the trials reporting zero events in both arms.[26,36] The results of these analyses are only reported if the conclusions differed from the primary analyses.

Cumulative meta-analyses are at risk of producing random errors because of sparse data and multiple testing.[37–40] Therefore, trial sequential analysis was performed to assess the robustness of the data.[41] The required information size was defined as the number of participants needed to detect or reject an intervention effect and was estimated on the basis of the event proportion in the control group, the observed relative risk reduction, and the diversity (model-based heterogeneity) of the meta-analysis.[38,42] The alpha was set to 5% and the power to 80%. On the basis of the required information size, trial sequential monitoring boundaries were constructed. Firm evidence was defined as being established if the sequential monitoring boundary was crossed before reaching the required information size. If the boundary was not crossed, the evidence was not conclusive.

Results

Overall, we identified 3044 references through our electronic searches and 17 references through manual searches (Figure 1). After excluding duplicates and references that did not refer to trials that fulfilled our inclusion criteria, 18 references (corresponding to 16 trials) were eligible for the qualitative data synthesis; 14 references (corresponding to 13 trials) fulfilled our inclusion criteria for the meta-analysis (Table 1).

Two trials were multicenter in design,[24,25] and the remaining were single-centered. The trials were all published as full articles from 1988–2003. One trial was published in Italian[43] and another trial in Spanish,[44] which also included a short publication in English.[45] The remaining trials were English language articles. Gallstones were diagnosed by ultrasonography. One trial used additional cholecystography,[46] and another used abdominal computed tomography scans.[47]

The 13 trials investigated obese participants (defined as BMI >30 kg/m^2) during weight reduction. The majority of participants were female (range, 42%–100%). Eight trials used caloric restriction (Supplementary Table 2) based on a low calorie diet (LCD) (900–1679 kcal/day) or VLCD ($<$800 kcal/day). The remaining 5 trials assessed weight loss after bariatric surgery.

Two trials compared a high-fat versus low-fat weight reducing diet.[35,48] The diet in the intervention and control groups included 12.2 g versus 3.0 g fat[48] or 30 g versus 2 g fat per day.[35] Overall, 11 trials assessed 300–1200 mg/day UDCA (median, 750 mg/day). The treatment duration ranged between 6 weeks to 18 months, and the duration of follow-up ranged from 6 weeks to 24 months. Two trials included 3 different doses of UDCA, 300/600/1200 mg.[24,25] Four trials included a third allocation arm in which participants received 1300 mg/day acetylsalicylic acid (aspirin),[23] 1600 and 600 mg/day ibuprofen, respectively,[26,27] or 11.3 g/day omega-3 fatty acids.[36]

Bias Control

None of the trials were classed as having a high risk of bias based on the allocation methods (Supplementary Figure 1). All trials apart from one of the dietary fat modification trials[48] were double-blind. Seven trials were classed as having a high risk of attrition bias because of incomplete data on patients lost to follow-up. This was considered the main source of bias in these trials. For 3 trials[24–26] the allocation group was not specified for participants with missing outcome data. All but 4 trials[23,26,35,46] included in the meta-analysis explicitly defined and reported all outcome measures. Three trials

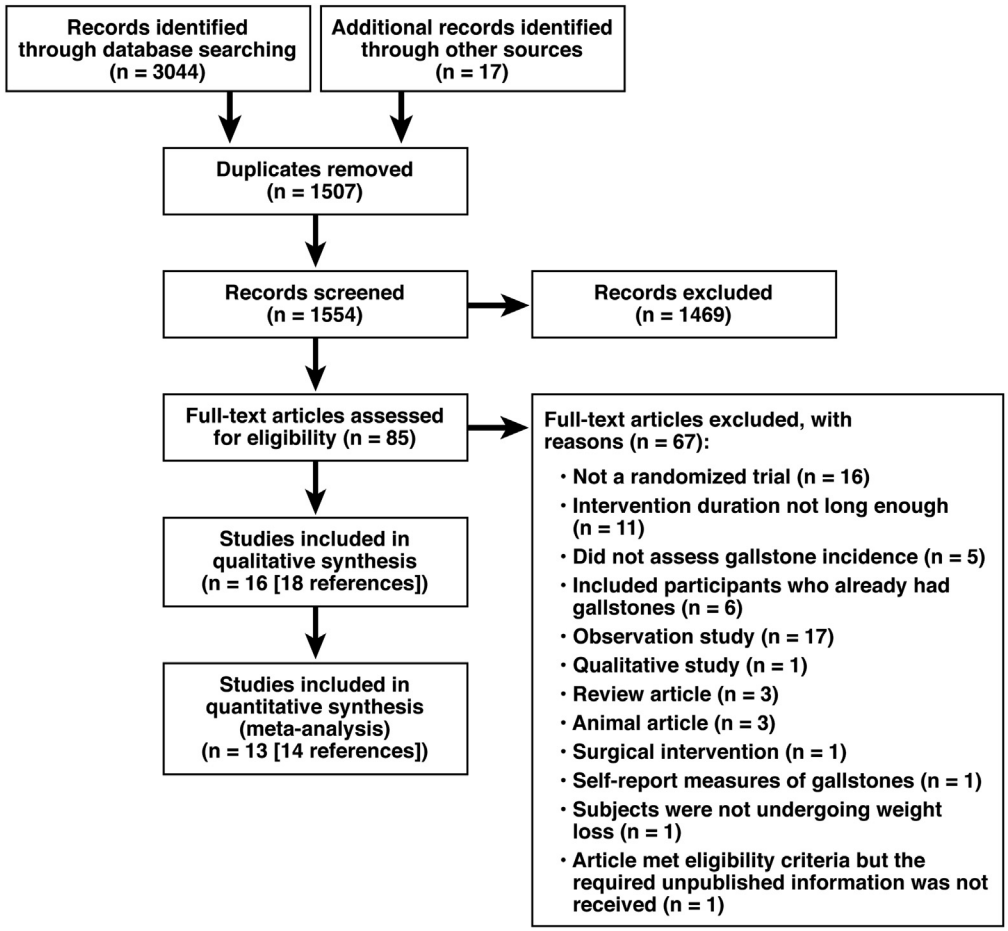

Figure 1. Flow chart for identification and selection of included randomized trials.

were either fully[24,25] or partially[35] funded by pharmaceutical companies. This funding did not obviously affect the overall trial design or analysis, because the trial design, dose, and duration of the interventions assessed did not differ from remaining trials. Two trials were terminated early because of high attrition and slow recruitment[26] or because the incidence of symptomatic gallstones was considered too high in the control group.[35] Five trials reported power calculations,[24,25,35,44,47] one of which did not achieve the expected power.[35]

Ursodeoxycholic Acid Interventions

As shown in Figure 2, 62 of 1217 participants (5%) in the intervention group and 130 of 574 (23%) in the control group of the 11 trials developed gallstones, corresponding to a RR of 0.33 (0.18–0.60, $I^2 = 65\%$). The corresponding NNT was 9 patients. No deaths were reported.

We were able to extract data on cholecystectomy because of symptomatic gallstone formation from 3 trials on UDCA versus controls.[24,47,49] Random-effects meta-analysis showed that UDCA reduced the risk of cholecystectomy for symptomatic stones, with a RR of 0.20 (0.07–0.53, $I^2 = 0\%$, NNT 15 patients; Supplementary Figure 2).

Because of differences in the assessment of bile lithogenicity, we were unable to perform meta-analyses on this physical-chemical outcome. Three of the trials assessing VLCD without bariatric surgery reported decreases of CSI in the UDCA-treated groups and increases in the placebo groups during follow-up as compared with baseline,[23,25,26] although this was only significant in 2 trials.[23,26]

Weight loss was described as being equal in the UDCA and placebo groups in all trials (range, 6–51 kg).[23–27,36,43,44,46,47,49] We were able to include data from 4 trials in a meta-analysis, confirming the finding of equal weight loss with WMD of −0.01 (−1.07 to 1.06, $I^2 = 0\%$).[23,25,36,44] Among the weight loss trials administering UDCA, Figure 3 illustrates that UDCA was more beneficial when only caloric restriction was used as compared with bariatric surgery (test for subgroup differences, $P = .03$). We did not have access to individual patient or trial level data for subgroup meta-analyses or meta-regression analyses on the relation between baseline weight or weight loss and intervention effects. However, the patient characteristics in the bariatric surgery trials indicated a higher baseline weight than those in the diet only trials (median, 143 vs 103 kg). The apparent weight loss was also larger in the bariatric surgery trials (median, 41 kg; range, 25–51) compared with dietary interventions (median, 10 kg; range, 6–25).

Table 1. Characteristics of RCTs of Nonsurgical Interventions for Primary Gallbladder Stone Prevention

Trial	Country	Patients (n)	Intervention (dose/day)	Intervention duration (*wk*)	Follow-up (*wk*)	Baseline weight (*kg*)	Mean weight lost (*kg*)	Percentage weight lost	Dropouts (excluding withdrawals)	Main inclusion criteria
Broomfield[23]	USA	23	VLCD + 1200 mg UDCA,	16	19	106	21	20	5	Obese
		22	VLCD + 1300 mg aspirin,			98	25	26	8	
		23	VLCD + placebo			106	21	20	4	
De Filippo[43]	Italy	20	LCD + 600 mg UDCA,	16	16	105	10	10	0	Obese
		20	LCD + placebo			101	8	8	0	
Festi[48]	Italy	16	VLCD + high-fat,	12	12[a]	115	20	17	5	Obese
		16	VLCD + low-fat			110	19	17	5	
Gebhard[35]	USA	7	LCD + high-fat,	12	12[a]	114	25	22	0	Obese
		6	VLCD + low-fat			105	23	22	0	
Marks[26]	USA	16	VLCD + 1200 mg UDCA,	12	12	100	10[b]	10	20[c]	Obese
		15	VLCD + 1600 mg ibuprofen,			110	11[b]	10		
		16	VLCD + placebo			114	11[b]	10		
Mendez-Sanchez[36]	Mexico	14	LCD + 1200 mg UDCA,	6	6	80	6	8	4[c]	Obese
		14	LCD + 11.3 g omega-3 fatty acids,			84	7	8		
		14	LCD + placebo			82	6	7		
Miller[47]	Austria	76	500 mg UDCA,	24	96	136	50	37	12	Obese
		76	Placebo			136	51	38	16	(after bariatric surgery)
Moran[44,45]	Mexico	18	LCD + 750 mg UDCA,	8	8	90	6	7	0	Obese
		18	LCD + 15 g fiber			86	6	7	0	
Shiffman[25]	USA	742	VLCD + 300/600/1200 mg UDCA,	16	16	128	25	20	255[c]	Obese
		255	VLCD + placebo			129	24	19		
Sugerman[24]	USA	231	300/600/1200 mg UDCA,	24	24[d]	137	40	29	72[c]	Obese
		74	Placebo			144	38	26		(after bariatric surgery)
Williams[46]	Canada	44	10 mg/kg UDCA,	Up to 72	Up to 72	—	40	—	6	Obese
		42	Placebo				43		0	(after bariatric surgery)
Worobetz[49]	Canada	13	1000 mg UDCA,	12	12	147	25	17	3	Obese
		16	Placebo			143	29	20	2	(after bariatric surgery)
Wudel[27]	USA	20	600 mg UDCA,	24	48	159	48	28	5	Obese
		20	600 mg ibuprofen,						5	(after bariatric surgery)
		20	Placebo						9	

[a]The entire study duration was 24 weeks; however, only the first 12 weeks were included in this systematic review because this was the weight loss phase.
[b]Weight loss reported only for the 6-week time point.
[c]Reported no significant difference between groups.
[d]54 patients were followed up for 48 weeks, but only data from the 24-week time point are included.

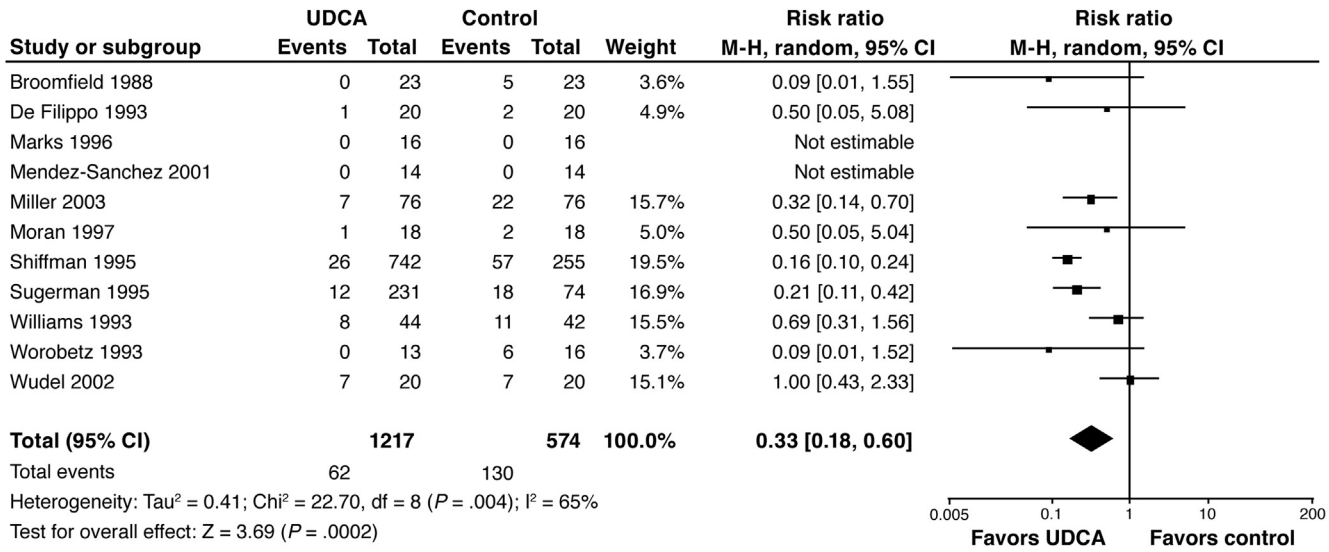

Figure 2. Meta-analysis of gallstone formation in obese patients receiving UDCA versus control interventions during weight loss. M-H, Mantel-Haenszel.

The type of bariatric surgery did not influence the effect of UDCA (test for subgroup differences, $P = .92$). Likewise, no difference was seen between trials that administered the lower or higher dose of UDCA (test for subgroup differences, $P = .12$). A subgroup analysis showed no difference between trials that initiated UDCA within the first week[24,27,47,49] or 6 weeks after surgery[46] (test for subgroup differences, $P = .26$).

There were no available data to assess quality of life. There was no difference between the UDCA trials with a low compared with a high or unclear risk of bias based on the subgroups of trials stratified by attrition bias ($P = .55$), reporting of outcomes ($P = .82$), or other biases ($P = .60$). The effect of UDCA was confirmed when the analyses were repeated by using good and poor outcome analysis ($P < .0001$ and $P < .00001$, respectively).

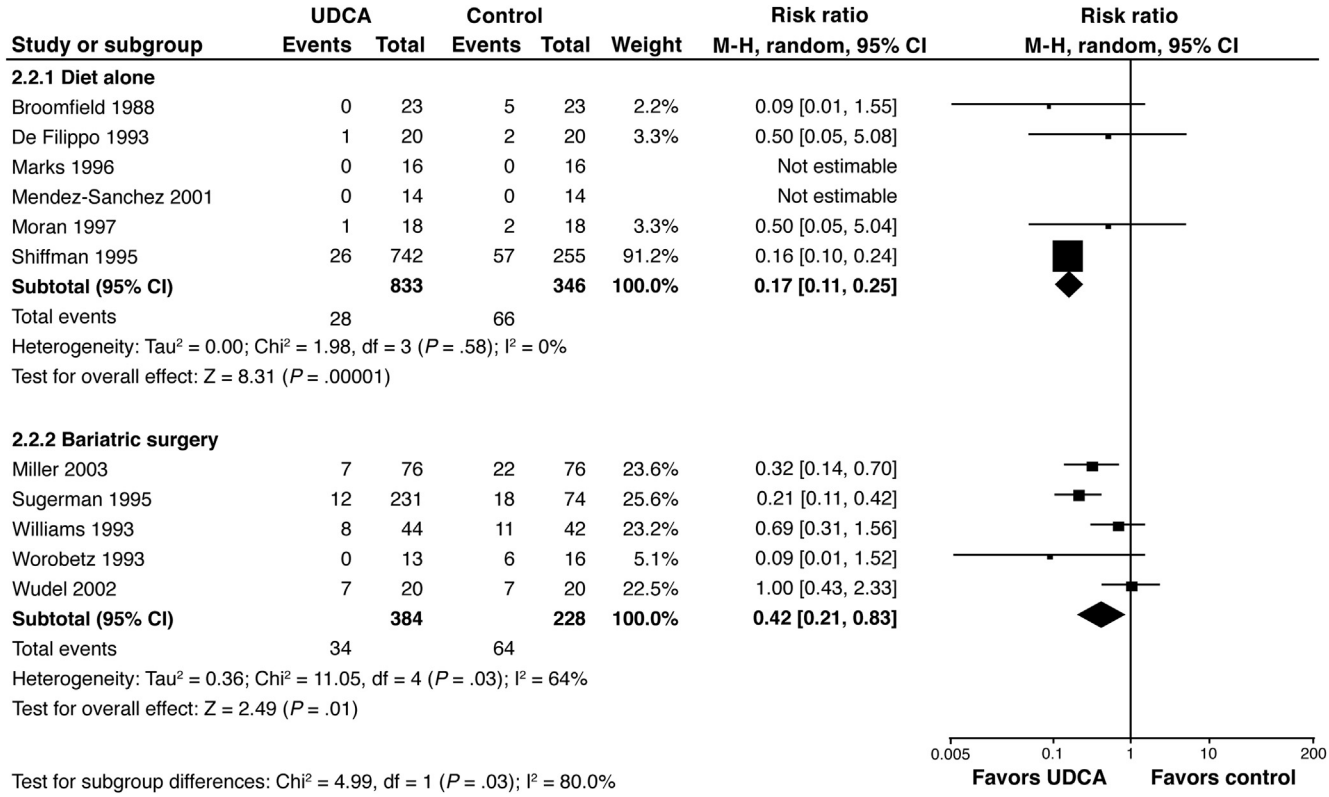

Figure 3. Meta-analysis of gallstone formation in obese patients receiving UDCA versus control interventions during weight loss with diet alone or after bariatric surgery. M-H, Mantel-Haenszel.

No evidence of small study effects was identified (Egger test, $P = .53$). In addition, trial sequential analysis was performed by using the trials assessing the efficacy of UDCA for gallstone prevention. On the basis of the findings from our random-effects meta-analysis (Figure 2), the incidence of gallstones in the control group was set to 23% (130 of 574) in trial sequential analysis; according to the model-based imputations for sequential analysis in the trial sequential analysis program, relative risk reduction was set to 67% and model-based heterogeneity (diversity) to 77%. This analysis did not confirm the result of the meta-analysis, because the trial sequential monitoring boundary was not crossed before reaching the required information size (not shown). This result suggests that the primary random-effects meta-analysis is not stable to adjustments for multiple testing and random error.

Interventions With Dietary Fat Modification

Two trials assessed high-fat versus low-fat weight loss diets. The weight loss in all groups ranged from 19–25 kg.[35,48] None of the 23 participants in the intervention group and 10 of 22 controls (45%) developed gallstones, 2 of which were symptomatic. Random-effects meta-analysis showed that high dietary fat intake during weight loss reduced gallstone risk (RR, 0.09; 0.01–0.61, $I^2 = 0\%$, NNT 2 patients). Quality of life was not assessed. Both trials reported a similar pattern in bile lithogenicity in both groups but did not report data that allowed meta-analyses. The trials described an initial increase in lithogenicity after both diets and subsequently a decrease to values lower than those at baseline during follow-up. We were unable to analyze the outcomes of cholecystectomy or weight loss because of differing reporting methods.

Other Interventions

The number of trials and participants assessing aspirin, ibuprofen, and omega-3 fatty acids was small, and few events were recorded. One trial[27] found that patients receiving ibuprofen formed gallstones at a higher rate than the placebo or UDCA groups. This was a trial with high attrition. Adverse events were not clearly reported. None of the remaining interventions demonstrated beneficial or detrimental effects (Table 2).

Table 2. Summary of Subgroup Random-effects Meta-analyses

Outcome or subgroup	Studies	n	Effect estimate, RR [95% CI]	Heterogeneity I^2, (%)
Gallstone formation in trials on diet alone or bariatric surgery using available case analysis	11	1470	0.34 [0.19–0.59]	66
Weight loss diet alone	6	949	0.17 [0.11–0.26]	0
Bariatric surgery	5	521	0.40 [0.22–0.74]	59
Gallstone formation in different types of bariatric surgery	5	612	0.42 [0.21–0.83]	64
Gastric bypass	2	345	0.45 [0.10–2.06]	87
Gastroplasty/gastric banding	3	267	0.42 [0.19–0.91]	38
Gallstone formation in relation to dose of UDCA	10	1728	0.21 [0.10–0.42]	66
UDCA 500–750 mg	6	930	0.29 [0.11–0.75]	73
UDCA 1000–1200 mg	6	798	0.11 [0.06–0.22]	0
Gallstone formation in relation to timing of UDCA initiation after bariatric surgery	5	612	0.42 [0.21–0.83]	64
Within 1 week	4	526	0.36 [0.15–0.83]	67
After 6 weeks	1	86	0.69 [0.31–1.56]	NA
Gallstone formation in relation to attrition bias	11	1791	0.33 [0.18–0.60]	60
Low risk of bias	5	562	0.26 [0.16–0.42]	0
High risk of bias	6	1229	0.38 [0.12–1.22]	86
Gallstone formation in relation to selective reporting	11	1791	0.33 [0.18–0.60]	65
Low risk of bias	8	1627	0.30 [0.16–0.57]	63
High risk of bias	3	164	0.38 [0.06–2.61]	51
Gallstone formation in relation to other bias	11	1791	0.33 [0.18–0.60]	65
Low risk of bias	5	291	0.28 [0.14–0.57]	0
High or unclear risk of bias	6	1500	0.38 [0.17–0.86]	81
Gallstone formation good outcome analysis	11	1791	0.39 [0.25–0.60]	37
Gallstone formation poor outcome analysis	11	1791	0.59 [0.51–0.68]	0
Aspirin versus placebo	1	45	0.42 [0.09–1.94]	NA
Aspirin versus UDCA	1	45	5.22 [0.26–102.93]	NA
Ibuprofen versus placebo	2	71	2.00 [1.03–3.88]	NA
Ibuprofen versus UDCA	2	71	2.00 [1.03–3.88]	NA
Omega-3 fatty acids versus placebo	1	28	NE	NA
Omega-3 fatty acids versus UDCA	1	28	NE	NA

NA, not applicable; NE, not estimable.

Table 3. Reported Adverse Events With UDCA Administration

Trial	Daily dose of UDCA (*mg*)	No. of adverse events in treatment group, % (n)	Type of adverse events in treatment group (n or %)	Type of adverse events in control group (n or %)
Mendez-Sanchez[36]	1200	13 (2)	Abdominal bloating and constipation (n = 2)	Abdominal bloating and constipation (n = 2)[a]
Miller[47]	500	8 (6)	Nausea, constipation (n = 6)[b]	Nausea, constipation (n = 2)[b]
Scott[50]	600	25 (17)	Nausea (n = 9) Diarrhea (n = 5) Dry skin/pruritus (n = 3)	Not reported
Shiffman[25]	300/600/1200	Not reported	Common complaints[b]: Constipation (27) Headache (27) Diarrhea (23) Dizziness (17) Upper respiratory infections (16) 13 patients withdrew because of adverse events	Common complaints[b]: Constipation (26) Headache (30) Diarrhea (24) Dizziness (16) Upper respiratory infections (13) 5 patients withdrew because of adverse events
Sugerman[24]	300/600/1200	Not reported	Vomiting or skin rashes[b]	Vomiting or skin rashes[b]
Williams[46]	10 (mg/kg)	9 (20)	Medication intolerance (n = 9)[b]	Medication intolerance (n = 7)[b]
Worobetz[49]	1000	8 (1)	Epigastric burning on medication ingestion and was withdrawn (n = 1)	

NOTE. Two of the trials included in the UDCA meta-analysis did not report on adverse events[23,27]; another 3 such trials[26,43,50] plus the trial by Mok[21,51] and the trial by Mazzella[52] included in the qualitative review found no adverse events in the UDCA groups.
[a]These adverse events were for the group receiving omega-3 fatty acids.
[b]No differences in adverse events between the placebo and intervention groups.

Adverse Events

No deaths were reported. UDCA did not increase the risk of adverse events (Table 3). Overall, few serious events were reported. The most common adverse events were gastrointestinal-related complaints. Only one[50] of the three[21,50–52] trials included qualitatively in this review reported adverse events with UDCA supplementation. No adverse events were described in the dietary fat modification trials.

Discussion

This systematic review suggests that UDCA and high-fat weight loss diets may be considered in the primary prevention of gallstones during weight loss. The number of patients who developed gallstones in the UDCA and control groups was 5% versus 23%, respectively. Our results suggest that about 9 patients have to be treated to prevent 1 patient from developing gallstones. The NNT to prevent 1 patient from forming gallbladder stones will depend on the baseline weight and absolute weight loss of the included patients. No effect on mortality was observed, and no major adverse effects were reported. The effects on bile lithogenicity could not be meta-analyzed, but some trials found improvements with UDCA administration. This is consistent with the reduced cholesterol supersaturation of bile, the physical-chemical prerequisite for lowering gallstone risk.[33]

The observed effect in our meta-analysis seemed to depend in part on the weight loss method, with patients after bariatric surgery having a smaller benefit than patients on diets alone. UDCA decreased gallstone incidence from 19% to 3% in the diet alone trials and from 28% to 9% in the post-bariatric surgery trials. A curvilinear relationship between the rate of weight loss in obese individuals and the incidence of gallstones has been observed,[53] with a weekly maximum of 1.5 kg being assessed as optimal to limit the risk. Other evidence indicates that a weight loss greater than 25% body weight increases stone risk significantly,[54] and this was observed in 3 of the bariatric surgery trials but none of the diet only trials. In addition, the higher baseline weight of the patients undergoing bariatric surgery might have contributed to statistical differences between the 2 groups of trials. Moreover, differences in intestinal and/or gallbladder motility, which may be modulated by UDCA,[55,56] could have contributed to these differences, with only some of the included trials reporting improved gallbladder contraction on UDCA administration.[23,26,27] The observed heterogeneity between trials mainly reflects differences between the bariatric surgery trials. This might have resulted from variations in UDCA dosage or length of therapy (range, 12–72 weeks) and follow-up (12–96 weeks); moreover, the post-surgery diet plans might have differed in terms of caloric composition and energy content.

In this review, a weight-reducing diet higher in fat (19%–30%) reduced the incidence of gallstones compared with one lower in fat (3%–5%). No adverse events were reported, but the trials had small sample sizes. A mechanistic rationale exists, because a diet higher in fat

stimulates gallbladder contractility and may ameliorate gallbladder hypomotility.[35] In fact, both trials reported significant decreases in gallbladder emptying on ingestion of a low-fat versus a high-fat meal during dieting.[35,48]

An important consideration is when to begin prophylactic therapy. Nonsurgical trials commenced UDCA therapy immediately on calorie restriction, whereas bariatric surgery trials initiated UDCA within days[24,27,47,49] or weeks.[46] Because gallstones may take approximately 4 weeks to develop,[15] preventive measures should begin immediately. Observational studies[55,57] report the incidence of gallstones to approximate 36% within 6 months after gastric bypass, and the incidence of gallstones stabilizes from there on (eg, at 12 and 18 months). Most of the UDCA interventions included in this meta-analysis lasted between 3 and 6 months, coinciding with when the majority of weight loss occurs. This could define the critical period for gallstone prevention in these patients.

We were unable to comment on the development of symptomatic gallstones in all included trials, but a subgroup analysis showed UDCA to reduce the risk of cholecystectomy, which was consistent with recent experimental findings[58] and some clinical observations.[59] Moreover, a recent meta-analysis concluded that prophylactic cholecystectomy during laparoscopic gastric bypass should be avoided in patients without gallstones because of the low necessity of subsequent cholecystectomy (<7%).[60] From a cost-effectiveness perspective, the decision to perform cholecystectomy to prevent gallstones, particularly in obese patients undergoing weight loss, depends on the incidence of gallbladder-related symptoms after surgery.[61] A study following 13,443 participants after bariatric surgery for 22 years reported a low incidence of gallstones, and the majority were asymptomatic.[62] Hence, a conventional nonsurgical approach for stone prevention may be preferred.

The small number of identified trials and correspondingly low sample sizes for some of the meta-analyses are the main limitation of this review. Several clinically relevant outcomes were also not addressed, in particular, quality of life measures. Moreover, a high risk of attrition bias was identified because several trials reported high dropout rates. The complexity with these trials is that participants were following a weight loss diet (as co-intervention) that, by default, yields high attrition.[63] It is possible that the poor compliance reflects the difficulty in following the weight loss diets rather than the interventions for primary stone prevention. In support of this, many trials did not find significant differences in attrition or in adverse events between the treatment and control groups. Finally, the data did not allow a meta-analysis of other interventions that reduce cholesterol precipitation in bile in preclinical or nonrandomized studies (eg, nonsteroidal anti-inflammatory drugs) with potential to prevent gallstones.[64]

Conclusions and Clinical Implications

Because both the obesity epidemic and weight loss interventions in obese patients increase the risk of gallstones, we will be faced with a higher incidence of gallstones. Nonsurgical options for the primary prevention of gallstones currently remain underused. Evidence-based guidelines are needed to guide preventive interventions for clinical practice. The meta-analysis herein suggests that UDCA and/or a diet higher in fat might decrease the overall risk of gallbladder stones forming during weight loss, albeit the subgroup of patients who goes on to develop symptomatic gallstones needs to be better defined. In future, multifactorial models based on the combination of clinical and genetic factors[65,66] might help in the precise identification of the patients who are at highest risk of symptomatic stones and likely to benefit most from nonsurgical gallstone prevention.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at http://dx.doi.org/10.1016/j.cgh.2013.11.031.

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Reprint requests
Address requests for reprints to: Frank Lammert, Prof Dr med, Department of Medicine II, Saarland University Medical Center, Kirrberger Str. 1, 66421 Homburg, Germany. e-mail: frank.lammert@uks.eu; fax: +49-6841-1623267.

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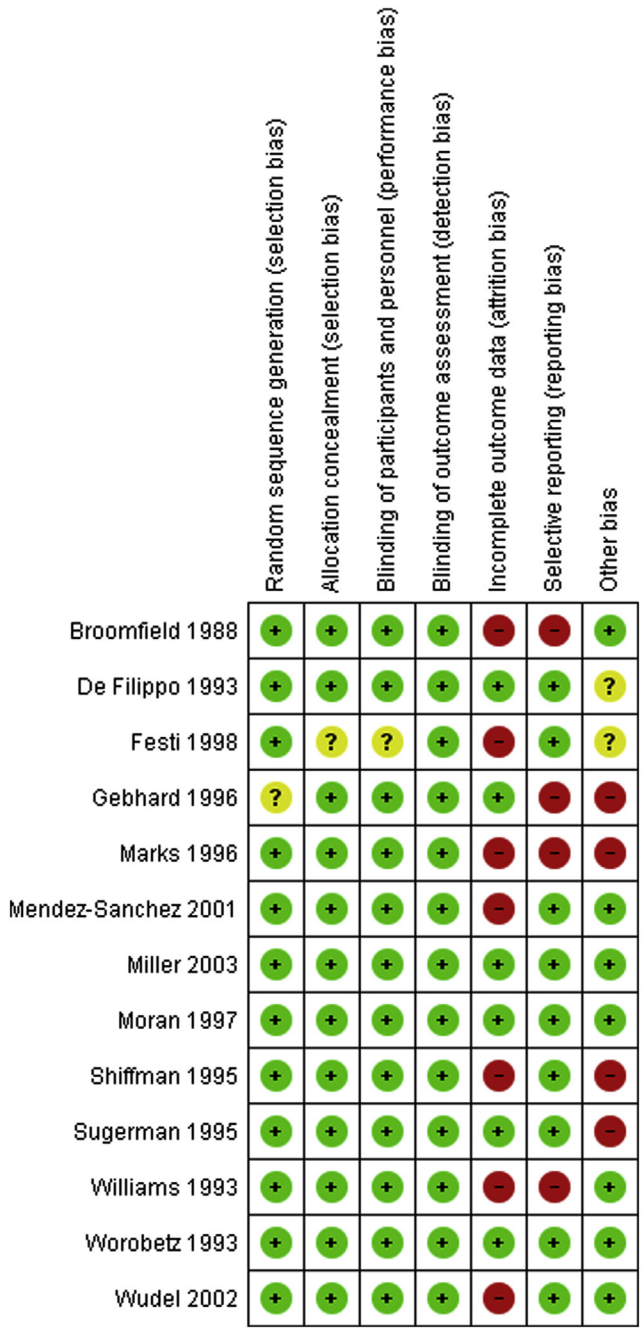
Conflicts of interest
These authors disclose the following: Frank Lammert has received lecture fees by the Falk Foundation e.V. Lise Gluud has participated in a trial funded by Merck. The remaining authors disclose no conflicts.

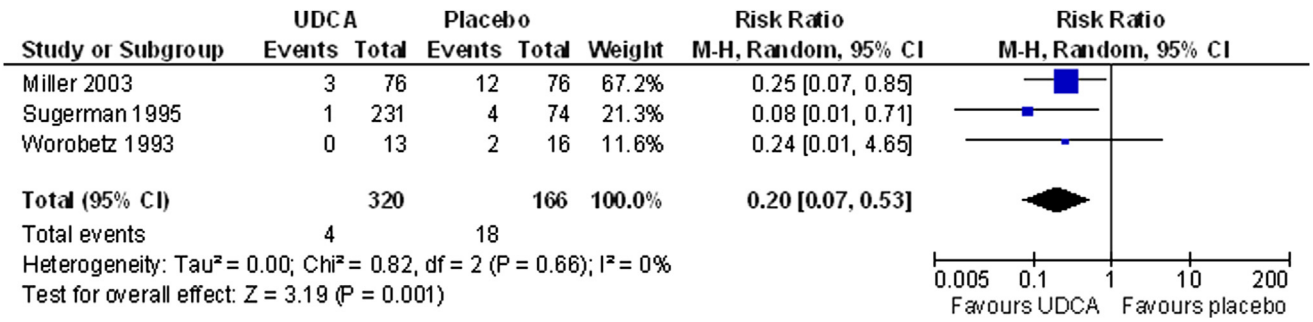


Supplementary Figure 1. Assessment of bias.

Supplementary Table 1. Full Electronic Search

#1 MeSH descriptor Ultrasonography explode all trees
#2 ultrasonograph* OR ultrasound* OR ecograph*
#3 (#1 OR #2)
#4 MeSH descriptor Ursodeoxycholic Acid explode all trees
#5 ursodeoxycholic acid* OR ursodiol OR UDCA
#6 (#4 OR #5)
#7 MeSH descriptor Anti-Inflammatory Agents, Non-Steroidal explode all trees
#8 (non-steroid* anti-inflammatory AND (drug* OR agent*)) OR ibuprofen OR aspirin
#9 (#7 OR #8)
#10 MeSH descriptor Obesity explode all trees
#11 obesity
#12 (#10 OR #11)
#13 MeSH descriptor Bariatric Surgery explode all trees
#14 bariatric surger*
#15 (#13 OR #14)
#16 MeSH descriptor Weight Loss explode all trees
#17 weight loss*
#18 (#16 OR #17)
#19 MeSH descriptor Diet Therapy explode all trees
#20 diet therap* OR caloric restriction OR low calorie diet* OR liquid diet* OR fat* OR protein* OR carbohydrate* OR fibre
#21 (#19 OR #20)
#22 MeSH descriptor Micronutrients explode all trees
#23 micronutrient*
#24 (#22 OR #23)
#25 MeSH descriptor Exercise explode all trees
#26 physical activit* OR exercise*
#27 (#25 OR #26)
#28 (#3 OR #6 OR #9 OR #12 OR #15 OR #18 OR #21 OR #24 OR #27)
#29 MeSH descriptor Cholelithiasis explode all trees
#30 cholelithiasis OR gallstone* OR gall* stone* OR 'black pigment stone*'
#31 (#29 OR #30)
#32 (#28 AND #31)

NOTE. Example given for the Cochrane Central Register for Controlled Trials in the Cochrane Library.



Supplementary Figure 2. Meta-analysis of obese patients requiring cholecystectomy after receiving UDCA vs control interventions during weight loss.

Supplementary Table 2. Dietary Composition of Weight Loss Diets

Trial	kcal	Protein (*g*)	Carbohydrates (*g*)	Fat (*g*)	Fiber (*g*)	Cholesterol (*mg*)
Broomfield[23]	520	55	79	1		
De Filippo[43]	1000–1200	60–70	100–170	20–43	35–40	165–220
Festi[48]						
Intervention	577	55	61.7	12.2		
Control	535.2	44.4	82.2	3		
Gebhard[35]						
Intervention	900	90	68	30		90
Control	520	50	76	<2		30
Marks[26]	520	NR	NR	NR		
Mendez-Sanchez[36]	1200	60	180	27		
Moran[44,45]	1679[a]	67	248	48	20	
Shiffman[25]	520	50	79	1–3		

NR, not reported.

[a]Each patient had to reduce their total energy intake by 500 kcal and was instructed to follow a diet with 15% protein, 60% carbohydrate, and 25% fat, as specified above.